Hepatitis C reinfection following treatment induced viral clearance among people who have injected drugs.

HEPATITIS C REINFECTION FOLLOWING TREATMENT INDUCED VIRAL CLEARANCE AMONG PEOPLE WHO HAVE INJECTED DRUGS

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ABSTRACT

BACKGROUND Although people who inject drugs (PWID) are an important group to receive Hepatitis C Virus (HCV) antiviral therapy, initiation onto treatment remains low. Concerns over reinfection may make clinicians reluctant to treat this group. We examined the risk of HCV reinfection among a cohort of PWID (encompassing all those reporting a history of injecting drug use) from Scotland who achieved a sustained virological response (SVR). **METHODS** Clinical and laboratory data were used to monitor RNA testing among PWID who attained SVR following therapy between 2000-2009. Data were linked to morbidity and mortality records. Follow-up began one year after completion of therapy, ending on 31st December 2012. Frequency of RNA testing during follow-up was calculated and the incidence of HCV reinfection estimated. Cox proportional hazards regression was used to examine factors associated with HCV reinfection. **RESULTS** Among 448 PWID with a SVR, 277 (61.8%) were tested during follow-up, median 4.5 years; 191 (69%) received one RNA test and 86 (31%) received at least two RNA tests. There were seven reinfections over 410 person years generating a reinfection rate of 1.7/100py (95%CI 0.7-3.5). For PWID who had been hospitalised for an opiate or injection related cause post SVR (11%), the risk of HCV reinfection was greater [AHR=12.9, 95%CI 2.2-76.0, p=0.002] and the reinfection rate was 5.7/100py (95%CI 1.8-13.3). **CONCLUSION** PWID who have been tested, following SVR, for HCV in Scotland appear to be at a low risk of reinfection. Follow-up and monitoring of this population is warranted as treatment is offered more widely.

ABBREVIATIONS PWID, People who inject drugs; HCV, Hepatitis C virus; SVR, Sustained viral response; PWUD, People who use drugs; RNA, Ribonucleic acid; ICD, International classification of diseases; CI, Confidence interval; HR, Hazard ratio; AHR, Adjusted hazard ratio.

KEYWORDS Hepatitis C virus, people who inject drugs, reinfection, sustained viral response, record linkage.

1. INTRODUCTION

The Hepatitis C virus (HCV) is one of the main causes of liver disease resulting in over 350,000 deaths per year worldwide (Perz et al., 2006). In resource-rich countries, the main route of HCV transmission is through injecting drug use. An estimated 16 million people currently inject drugs worldwide (Mathers et al., 2008) and the majority (>60%) have been infected with HCV (Nelson et al., 2011). Despite favourable treatment outcomes among, and indeed guidelines (EASL, 2014) recommending prioritisation for, people who inject drugs (PWID) (Aspinall et al., 2013), initiation onto treatment in this population remains low (Iversen et al., 2014). The risk of HCV reinfection following a sustained viral response (SVR) among this group remains a concern, causing reluctance among some clinicians to treat these individuals. Several studies have considered HCV reinfection among PWID following SVR (Dalgard et al., 2007; Backmund et al., 2004; Currie et al., 2008; Grebely et al., 2010; Grebely et al., 2012; Grady et al., 2012) and, in a meta-analysis, Aspinall *et al.* (2013) estimate the rate of HCV reinfection following SVR to be 2.4/100 PY among 131 people who use drugs (PWUD) and 6.4/100 PY among 45 active PWID. Uncertainty around these estimates remains due to the small sample sizes involved and the predominant focus on harm reduction and substitution therapy in follow-up PWID studies.

In Scotland there has been a 2.7-fold increase in the number of people initiated on therapy between 2007 (N=470) and 2014/2015 (N=1,270), related to the sustained financial investment by the Scottish Government in the treatment of hepatitis C (Scottish Government Health Department 2006, 2008 and 2011; Health Protection Agency, 2015). The proportion of treatment initiates with a history of injecting drug use has also increased from 65% to 83% over the same period (Health Protection Agency, 2015). With the new 'patient friendly' therapies in our midst (involving short treatment duration, clearance rates of 90% and higher, simple oral-only regimens and minimal side effects), the potential to expand treatment further

in this high risk population is significant. Guidelines state that following SVR, PWID who continue to practise behaviours that put them at risk of reinfection, should be tested annually for HCV RNA (EASL, 2014). However, little is known on the extent of testing and reinfection among patients following SVR attainment. To gain a better understanding of the potential risk of reinfection among those who have reported a history of injecting drugs, we adopted a novel record-linkage approach of retrospective national HCV clinical and test data to uniquely investigate HCV testing practice following SVR and examine the incidence of HCV reinfection, and associated risk factors, among PWID in Scotland.

2. METHODS

2.1 Study population and data sources

This retrospective cohort includes individuals who were diagnosed with chronic hepatitis C and attained a SVR after commencing therapy between 1st January 2000 and 31st December 2009, in one of four large health boards in Scotland (Greater Glasgow & Clyde, Grampian, Lothian or Tayside; representing 73% of new HCV diagnoses in Scotland from 2002-2012), and who reported injecting drug use as a risk factor for their HCV infection (n=~~*565*~~*570*). A sustained viral response is associated with viral clearance and is defined as undetectable HCV RNA (i.e. negative RNA) six months after completion of antiviral therapy. It is not known if individuals continued to inject during study follow-up, however they will be referred to as PWID from this point onwards. The cohort were identified from the Scottish HCV clinical database, held at Health Protection Scotland, which contains demographical, clinical and virological information on all patients who have ever attended a HCV treatment clinic in Scotland. Key data such as risk information, genotype (where available), cirrhotic state, start and end dates of antiviral therapy, treatment regime and treatment centre are held on this system.

To identify RNA test records for our study cohort, the Scottish HCV test database, also held at Health Protection Scotland, was used. Retrospective laboratory test data from the four largest health boards in Scotland (Greater Glasgow & Clyde, Grampian, Lothian and Tayside) are stored in the HCV test database (Shaw et al., 2003; McLeod et al., 2014). Test data were available from 1st January 1999 to 31st December 2012 and included specimen date, test results, demographic information and additional details relating to the test. PWID with a SVR were deterministically linked to the HCV test databases, using exact matching of patient identifiers; sex, date of birth, first initial and the soundex code of the surname.

The adopted time frames described above, allowed us to systematically search for a positive RNA test prior to treatment and a negative RNA test within 3-12 months post completion of therapy (the RNA test closest to 6 months post completion of therapy was regarded as the SVR test) for each individual in the cohort. Patients who did not have a positive RNA test prior to treatment or a negative RNA test within 3-12 months of completing therapy, were excluded (*n*=~~206~~*125*). These criteria ensured that individuals in the cohort had a history of injecting drug use and cleared their HCV infection after successful treatment.

The cohort was probabilistically linked to hospital admission data to identify injection-related hospital episodes, and mortality data to censor our analysis at death. These data are held by colleagues at Information Services Division. Hospital admission and discharge dates, admission type, details on patient condition (as classified under ICD-9 & ICD-10), date of death and cause of death (as classified under ICD-9 & ICD-10) were extracted. We specifically looked for hospital admissions with ICD codes relating to opiate and/or injecting drug use, as an indicator of continued injecting drug use, post SVR; the same admission codes described by Valerio *et al*. (2015) are applied here and relate to opiate use: *mental and behavioural disorders due to opiate* misuse (ICD-10: F11), *poisoning due to*

opium (ICD-9: 965.0; ICD-10: T40.0), *poisoning due to heroin* (ICD-10: T40.1), *accidental poisoning due to heroin* (ICD-9: E8500; ICD-10: X42.4) *accidental poisoning due to opium* (ICD-10: X42.9), *intentional self-poisoning by exposure to opium* (ICD-10: X62.9), *opiate dependence* (ICD-9: 3040), *non-dependent opiate use* (ICD-9: 3055), *finding opiates in blood* (ICD-10: R781), and injecting behaviour; *endocarditis* (ICD-9: 421.0; ICD-10: I33), *deep vein thrombosis* (ICD-9: 451, 453 ; ICD-10: I80), *cellulitis /abscesses* (ICD-9: 682; ICD-10: L02, L03).

Study follow-up began one year after completion of therapy, to ensure that RNA tests relating to SVR were not included in the analysis, and ended on 31st December 2012. Individuals who were known to have died prior to the start of follow-up were excluded (*n=2*).

2.2 Statistical analysis

Deterministic record linkage, data manipulation and statistical analyses were performed using statistical software packages R, version 3.03 (R Core Team 2014), Stata, release 9 (StataCorp 2005. College Station, TX, USA) and database system PostgreSQL, version 1.14.3 (The pgAdmin Development Team, 2012).

2.2.1 Frequency of, and factors associated with HCV RNA testing

The frequency of RNA testing during study follow-up was investigated and Cox proportional hazard regression was used to examine differences between those who did and did not receive a RNA test. Time at risk begins one year after completion of therapy (to allow up to 9 months for SVR eligibility and then up to three months to receive that SVR test) and ends at earliest date of first RNA test, date of death or 31st December 2012. Kaplan Meier survival

analysis was used to estimate the cumulative proportion tested for RNA within the first three years of follow-up post SVR.

2.2.2 Incidence rate of, and factors associated with Reinfection

All PWID who received at least one RNA test during study follow-up were considered in this analysis. HCV reinfections were defined as a positive RNA result during study follow-up and the time of reinfection was estimated to be the midpoint between the last negative and the first positive RNA results. Time at risk began one year after completion of therapy and ends at earliest date of reinfection, last negative RNA test (for PWID who are not reinfected) or date of death. The incidence of HCV reinfection was expressed in terms of person years. Associated risk factors were analysed using Cox proportional hazards regression.

3. RESULTS

3.1 Study cohort

Between January 2000 and December 2009, 448 PWID were eligible for inclusion into the study cohort. The majority were men (77%) aged greater than 35 years old at the start of treatment (mean age 38 years with standard deviation ± 8 years, range 18-66 years) and most individuals commenced therapy between 2006 and 2009 (66%). Pegylated interferon (Peg IFN) and Ribavirin was the treatment regime for 97% of the cohort. Thirty-one PWID (7%) were cirrhotic at the start of treatment and 95% were treatment naive. In terms of potential risk behaviour, 33% and 10% of PWID had been admitted to hospital with an opiate or injection related cause pre treatment and during follow-up respectively. The mean follow-up, from cohort entry to 31st December 2012, was 4.5 years (range 181 days - 11.9 years) involving a total of 2,014 person years.

3.2 Frequency of, and factors associated with HCV RNA testing

The frequency of HCV RNA testing during follow-up is described in Figure 2. Two individuals died during the first year of the follow-up period leaving 446 PWID available for testing, of which only 214 were tested (48%). The proportion of PWID tested continued to decrease during follow-up, with ≤10% receiving a RNA test during the 4th and subsequent years of follow-up.

Follow-up time to first RNA test (Table 1), was 910 person years (average 2.0 years, range 1 day - 9.8 years), during which 277 PWID received at least one RNA test and 413 RNA tests were carried out during the study period. The Kaplan Meier estimate of the entire cohort tested for RNA within the first three years of follow-up was 59.9% (95% CI 55.2-64.6). Strong associations with the frequency of RNA testing were observed among PWID who; were cirrhotic at the start of therapy [AHR=1.86 with 95% CI 1.15-3.00], commenced therapy in recent years i.e. from 2003 to 2005 [AHR=0.67 with 95% CI 0.43-1.03] and from 2006 to 2009 [AHR=0.50 with 95% CI 0.33-0.76] relative to those who commenced therapy between 2000-2002.

3.3 Incidence rate of, and factors associated with Reinfection

Of the 277 PWID who had at least one RNA test during follow-up, there were seven (2.5%) reinfections (Table 2). A total of 28 RNA tests were carried out among these individuals. Of the seven reinfections, four had only one positive RNA test during follow-up, two individuals had two positive RNA tests and one individual had three consecutive positive RNA tests. Genotype data was available for all primary infections and four reinfections. For all four cases where the genotype of the reinfection was known, a genotype switch was observed when compared with the primary infection.

The total follow-up time in our reinfection analysis was 410 person years (average 1.5 years, range 1 day - 8.9 years). The overall estimated incidence rate of reinfection was 1.71/100 PY [95% CI 0.69-3.52]. The incidence of reinfection among PWID who had an opiate-related hospitalisation pre treatment, 3.36/100 PY (95% CI 1.09-7.83), was 4 times larger than in those who had not, 0.77/100PY (95% CI 0.09-2.77) [AHR=2.44 with 95% CI 0.41-14.37]. The incidence of reinfection among those who were admitted to hospital with an opiate or injection related cause during study follow-up was 5.68/100 PY (95% CI 1.84-13.26); substantially greater than those who were not admitted (0.62/100 PY) [AHR=12.89 with 95% CI 2.18-73.21].

4. DISCUSSION

Data on the incidence rate of HCV reinfection following treatment induced viral clearance among PWID is limited. A recent meta-analysis identified five prospective studies where PWID were followed up after successfully completing treatment for their HCV infection (Aspinall et al., 2013). With a combined sample size of 131 individuals, the incidence of HCV reinfection was estimated to be reasonably low at 2.4/100 PY among people who had ever injected drugs (includes individuals who have ceased injecting and active injectors) and 6.4/100 PY among people who reported injecting drug use post SVR. Using a unique retrospective record linkage study design, we estimate similar rates of reinfection to be 1.7/100 PY among people who have ever injected and 5.7/100 PY among those with behaviours suggesting ongoing drug use (based on hospital admission data). Higher reinfection rates have been reported among PWID in the prison setting; 5.3/100 PY overall and 12.5/100 PY among active PWID (Marco et al., 2013). The risk of reinfection found among PWID who were hospitalised with an opiate or injection related cause during the study follow-up period [AHR 12.89 with 95% CI 2.18-76.04] was greater than that found

among those who were not hospitalised; suggesting this measure is a reasonable proxy for continued injecting drug use and risk behaviour in this group. However, since we did not have information on current injecting status during follow-up, these results may not be generalisable to all or active PWID.

Drawing on data on the average incidence of HCV infection among active PWID in the Scottish community, estimated to be 10.0/100 PY across the 2008/09, 2010 and 2011/12 sweeps of the Needle Exchange Surveillance Initiative (University of the West of Scotland et al, 2008/2009; 2010; 2011/2012), would suggest that individuals in this study, who have undergone treatment and successfully cleared their infection, had in comparison fewer injecting risk behaviours post SVR; it's plausible that many in the cohort had indeed ceased injecting prior to commencement of treatment. However there remains at least a minority of individuals who continue to behave in a way that puts them at risk of becoming reinfected, also observed by Valerio *et al.* (2015), and these individuals must be identified and closely monitored via periodic RNA testing as suggested in the EASL guidelines (EASL, 2014). Our data suggest that the frequency of RNA testing, post-SVR, among successfully treated PWID has decreased over time; PWID treated recently i.e. 2006-2009, were 50% less likely to receive an RNA test when compared with those treated during 2000-2002. To adhere to recent clinical guidelines on annual HCV re-testing for those at risk (EASL, 2014), a coordinated approach (involving practitioners in specialist care, general practice and addiction services) will undoubtedly be required to ensure an increase in testing among this group, and a more comprehensive assessment of the risk of HCV reinfection will be possible.

This study has the following limitations. Firstly, the reinfection studies reviewed by Aspinall *et al.* (2013) used prospective cohort designs, which have the advantage of closely monitoring individuals over time and frequent testing of HCV RNA is possible. In general, PWID are not routinely tested for RNA post SVR and 38.2% of the cohort (N=171) were

never tested during follow-up in this study. Of those who were tested, 69% received just one RNA test. This may be an accurate representation of the frequency of RNA testing post SVR in Scotland however we must acknowledge that the linkage process is not perfect and RNA tests may not have been identified due to lack of identifiers in the HCV test database (12.9% of HCV test records do not have complete identifiers i.e. sex, date of birth, soundex code of surname and first initial, which are required for deterministic linkage) and therefore RNA testing among this group may be underestimated (Kendrick and Clarke, 1993).

Ideally two consecutive positive RNA tests would be required to confirm reinfection (Scottish Intercollegiate Guidelines Network, 2013). In this analysis, at least two positive RNA tests were identified during follow-up for three reinfections, however due to limited testing data, the classification of a reinfection relied on one positive RNA test for the remaining four reinfections. Among four PWID with possible reinfection (including one with only one positive RNA test), a genotype switch was observed between the primary and secondary infections giving further support to these being true reinfections. Hara *et al.* (2015) have shown that small levels of HCV can persist for years following treatment induced viral clearance (based on interferon based therapy) and therefore 'reinfections' from a new virus may actually be late relapses due to the original strain detected before treatment. Sequence typing would be preferable to prove reinfection beyond doubt; however sequence data were not available in this analysis. Approximately 38% of the eligible cohort (171 out of 448, Figure 1.) were not included in the analysis of reinfection because HCV RNA tests could not be identified during follow-up. Similar to those who were included, 10% of these individuals had been admitted to hospital with an opiate or injection related cause during follow-up, therefore the reinfection rate for this group is likely to be similar to that presented. However, hospital admission data was not available for 122 PWID who were excluded from the study and estimates of ongoing risk behaviour in this group is unknown.

Of the four reinfections where a genotype switch was observed, two were also successfully treated for the second time and cleared their reinfection during follow-up. Both individuals were treated with Peg IFN and Ribavirin for the initial infection and reinfection. Treatment courses are reasonably long and side-effects associated with Peg IFN therapy can be severe (Scottish Intercollegiate Guidelines Network, 2013) and may be viewed by some as a deterrent against risk behaviours associated with reinfection. The new therapies coming onto the market are highly effective (~90% clearance rate) (Scottish Medicines Consortium, 2015), follow simple one pill regimens and are interferon free therefore have minimal side effects. Widespread use of these new therapies will take time due to the high associated costs; however having access to a simple oral regimen with a high chance of clearance may not dissuade people against risking reinfection in the future. A degree of risk complacency has been observed in the context of HIV, where there is some evidence suggesting that young men who have sex with men (MSM), who had never tested for HIV or had last tested HIV negative, are less concerned about becoming infected with HIV because of antiretroviral therapy (ART), and are therefore more likely to engage in risk behaviours associated with the acquisition of HIV (MacKellar *et al*. 2011a, 2011b).

Looking to the future, the frequency of RNA testing among PWID will increase if the new EASL guidelines (EASL, 2014) are adopted i.e. annual RNA testing among those who continue to inject post SVR, and it remains to be seen how this will impact on the number of HCV reinfections identified. Using mathematical modelling Vickerman *et al*. (2012) explain that long time intervals (>3 months) between testing may underestimate reinfection rates; the model considered spontaneous resolvers only, but this may also be applicable to those who clear their infection following successful antiviral therapy. Therefore, even if annual testing among PWID following successful treatment becomes routine, we may still underestimate the number of individuals who are reinfected due to the length of time between tests.

4.1 Conclusions and recommendations

This study applied a novel approach to estimate HCV reinfection following treatment induced viral clearance among a group of individuals reporting injecting drug use as a risk factor for their initial infection. The results highlight a possible issue in terms of the lack of routine testing among PWID post SVR; however it is hoped that more frequent testing will occur in light of the new EASL guidelines (EASL, 2014) and in turn this will help identify HCV reinfections in a timely manner. Using opiate and/or injection related hospital admissions as a proxy for continued injecting drug use post SVR, we found that a reasonable proportion (at least 10%) of individuals continue to inject at a high intensity. For individuals who are known to have ever injected drugs, provision of harm reduction services such as education on risk behaviours, needle and syringe exchange programmes and opiate substitution therapy should be available alongside and following treatment. Reinfection rates among these individuals is comparable to other estimates reported in the literature, however we are the first to adopt record linkage techniques and use "real world" administrative health data to tackle this question. These data support the consensus view that the rate of reinfection among this population, on the whole, is low. Reinfection should not therefore be seen as a barrier to treating PWID with antiviral therapy.

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Table 1. Relative risk of receiving at least one HCV RNA test among PWID during study follow-up, where time at risk begins one year after completion of therapy and ends at earliest date of first RNA test, date of death or 31st December 2012.

Table 2. Detection of HCV reinfection among PWID who have received at least one RNA test during study follow-up, where time at risk begins one year after completion of therapy and ends at earliest date of reinfection (midpoint between last negative RNA test and first positive RNA test), last negative RNA test (for PWID who are not reinfected) or date of death.

Fig 1. Schematic diagram of study cohort.

Fig 2. Frequency of HCV RNA testing during study follow-up. Total number of PWID in each year of study follow-up is given in brackets (excluding those who died during or prior to that year).